EFFICACY OF PIPPALI (PIPER LONGUM) IN IMPROVING PRIMARY HYPOTHYROIDISM: RANDOMIZED CLINICAL TRIAL

Synopsis

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Submitted by

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1. INTRODUCTION

1.1 THYROID DISORDERS

Thyroid diseases are the common endocrine disorders worldwide. Hypothyroidism can manifest due to thyroid gland failure; deficiency of thyroid releasing hormone (TRH), TSH, or both; iodine insufficiency. Depending upon the cause of the disease, hypothyroidism can further be segregated into the following types: Primary hypothyroidism and Secondary Hypothyroidism (Singh, B. et.al., 2021). The conventional approach to the treatment of hypothyroidism relies on the use of levothyroxine replacement therapy. The therapy is known to cause impairment in the neurocognitive functions that lead to poor quality of life and life-long treatment causes poor patient compliance. The thyroid produces approximately 90% inactive thyroid hormone, or thyroxine (T4), and 10% active thyroid hormone, or triiodothyronine (T3) (Yasoda A. 2018). Inactive thyroid hormone is converted peripherally to either activated thyroid hormone or an alternative inactive thyroid hormone. T3 is responsible for affecting many organs and tissues throughout the body, which can, in summary, be the effect of increasing metabolic rate and protein synthesis.

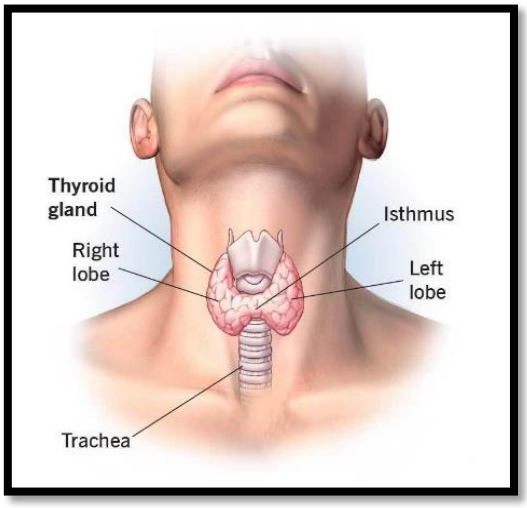

Fig. 1 Thyroid Gland Depiction

The prevalence of hypothyroidism in the developed world is about 4-5%. The prevalence of subclinical hypothyroidism in the developed world is about 4-15% (Unnikrishnan G.A. et.al., 2013). According to research conducted, it has been estimated that about 42 million people in India suffer from thyroid diseases (Unnikrishnan G.A. et.al., 2011). The incidence of congenital hypothyroidism in the screening of nearly 40,000 newborns is about 1 in 2,640, which is much higher than the worldwide average of 1

in 3,800. Diagnostic delay in hypothyroidism is common and is related to a lack of awareness amongst primary health care practitioners and family physicians as well as the cost and availability of laboratory investigations (Desai P.M. 1997).

THYROID RANGE

Table 1 The table shows the normal range of thyroid profile.

TEST NAME (THYROID PROFILE)	NORMAL RANGE	OPTIMAL RANGE	UNIT
T3	0.79-2.0	0.8-2.0	ng/mL
T4	4.5-9.8	4.5-9.8	µg/dL
TSH	0.45-4.12	0.5-2.5	mIU/mL

Zulewski's Clinical Score

Zulewski's clinical scoring is an economical and effective tool for identifying clinical hypothyroidism and can be used as a clinical basis for starting levothyroxine replacement therapy if due to unavoidable reasons, it is difficult to get a thyroid function test. Hypothyroidism is a common endocrine disorder with several comorbidities. Biochemical testing is ideal for diagnosis of hypothyroidism. Still, clinical scores such as Zulewski's score may be used as valid and economic aids for planning and starting the levothyroxine replacement therapy in cases where biochemical testing cannot be performed, or there is a disparity between clinical and biochemical finding, and also it can be used as a mass assessment tool to prevent delay in instituting therapy to those who need it (Srivastava, P. 2020).

Table 2 Zulewski's Clinical Score

Sign/ Symptoms	Identification on the basis of	Point given if present
Signs		
Slowness of movements	Observing patient walking and sitting in the OPD room, also getting ready for examination process	1
Ankle reflex	Observing relaxation	1
Coarse skin	Dermatologist finding on examining skin of the hand, forearm, and elbow for thickness and roughness	1
Periorbital puffiness	Observing periorbital swelling	1
Cold skin	Comparing temperature of hand with examiners	1
Symptoms		
Diminished sweating	Questioning regarding sweating in normal or warm room	1
Hoarseness of voice	Questioning regarding changes in speaking or singing voice	1
Paresthesia	Questioning regarding subjective sensations	1
Dry skin	Questioning regarding dryness of skin and requiring treatment inform of moisturizing	1

	agent	
Constipation	Questioning regarding bowel habits and use of laxatives	1
Hearing treatment	Questioning regarding the difficulty in heating	1
Weight increase	Questioning regarding increase in weight	1

1.2 PIPPALI- THE POWERFUL HERB

Fig. 2 Pippali Plant

Fig. 3 Dried Pippali

Pippali is also known as Long pepper and Piper longum (Sharma. L. et.al., 2018). The most utilized parts of this plant are mainly fruits and roots. Long pepper (Pippali) can be classified into Kingdom (Plantae), Division (Magnoliophyta), Order (Piperales), Family (Piperaceae), Genus (Piper), and Species (Longum). The pepper word is obtained from sanskrit word for long pepper (pippali). It is a thin and redolent climber. Pippali is a flowering plant, it has a pungent and sweet taste at the same time. It is mostly used as a spice and seasoning and as a drug in Europe during the medieval period and in the 19th century. Theophrastus categorized pepper into two divisions i.e., round one and another long one. Medicinally, the plant is reported as a good remedy to cure menstrual pain, gonorrhea, sleeping problems, tuberculosis, respiratory tract infections, arthritic conditions, and chronic gut-related pain (Grover. M. et.al., 2021). It is also used as a preservative in pickles, food products, medicine, and traditional drinks. Regional names are- *Pippali, Pipar, Pipal in* Hindi*; Hippali, Thippali bali in* Kannada*; Tippali, Pippali in* Malayalam*; Pimpli in* Marathi; *Tippili in* Tamil; *Pippallu, Pippali in* Telegu; *Ushana, Kana, Magadhi, Pippali, Krishnapippali in* Sanskrit; *Pipul in* Bengali*; Long Pepper in* English*; Lindi Pepper in* Gujarati; *Pippalimula in* Orissa*; Maghan in* Punjabi*; Filfil Daraz in* Urdu. The long pepper is a perennial plant lasting for three seasons or more. The root of the plant is also known as Pippalimulam. The colour of the pippali riped fruit is red and when it dries the colour converts into

black. It is cultivated in hot and temperate areas (Assam, Tamilnadu, and Andhra Pradesh) of India. Piper longum was cultivated from the lower hills of Bengal, evergreen forests of western ghats, Uttar Pradesh Nicobar Islands, and Nepal. It is cultivated on a large scale in limestone soil and where dampness is high in heavy rainfall areas. Laterite soil is suitable with good water-holding capacity and organic matter content. The main active constituents present in P. longum plant are alkaloids which include piperine, piperlonguminine, piperlongumine and methyl-3,4,5- trimethoxycinnamate (Chatterjee A. et.al., 2001). The fruit part consists of volatile oil (1%), protein, starch, alkaloids, saponins, carbohydrates and amygdalin, a waxy alkaloid isobutyldeca-trans-2-trans-4-dienamide, alkaloids piperine, calcium, phosphorus, iron, and a terpenoid substance. The root part of the plant contains piperlongumine or piplartinine, piperine and dihydrostigmasterolasarinine, pellitorine, refractomide A, brachystine, pipercide, piperderidine, piperundecalidine, iperonaline, methyl piperine, terahydropiperlongumine, dehydropipernonaline piperidine, trimethoxy cinnamoyl-piperidine and piperlongumine (Grover M. et.al., 2021). Indian long pepper, or pippali, is rich in alkaloids, beta sitosterol, and analgesic. It also has a ton of eugenol, glycosides, piperine, resins, sugar, saturated fat, essential oil, volatile oil, piplartine, myrcene, terpenoids, quercetin, triacontane, and sylvatine. These are all essential nutrients and compounds present in long pepper that contribute to the better functioning of entire body system.

1.3 MECHANISM OF ACTION

The herbal approach and its bioactive constituents came up as a suitable alternative for hypothyroidism. In this context, Costuspictus belonging to the family Costaceae, also termed as the insulin plant because of its utility for diabetes management has shown potential application for alleviating hypothyroidism. The concoction restores normal thyroid levels and improves the thyroid profile (Ashwini, S. et.al., 2017). Owing to the predominance of Kapha and Vata Dosha along with deranged metabolism, Pippali which mainly possesses VataeKaphahara with Agni deepana (Bio-fire enhancer) and Rasayana (Rejuvenating) properties seems to be promising in Hypothyroidism. Studies suggest Vardhamana Pippali Rasayana acts by correcting Agni, does purification of microchannels by exerting Vata kaphahar property, and by increasing supply and assimilation of micronutrients to tissues in Hypothyroidism (Singh S. et.al., 2015). Piperine is known for its easy diverging and increasing permeability by regulating membrane active. A

study reported that combination of three pippali increased their bioavailability by encouraging fast absorption from the gastrointestinal tract or by metabolism during its first passage through liver after being absorbed, or by both mechanisms (Shamra L. et.al., 2018).

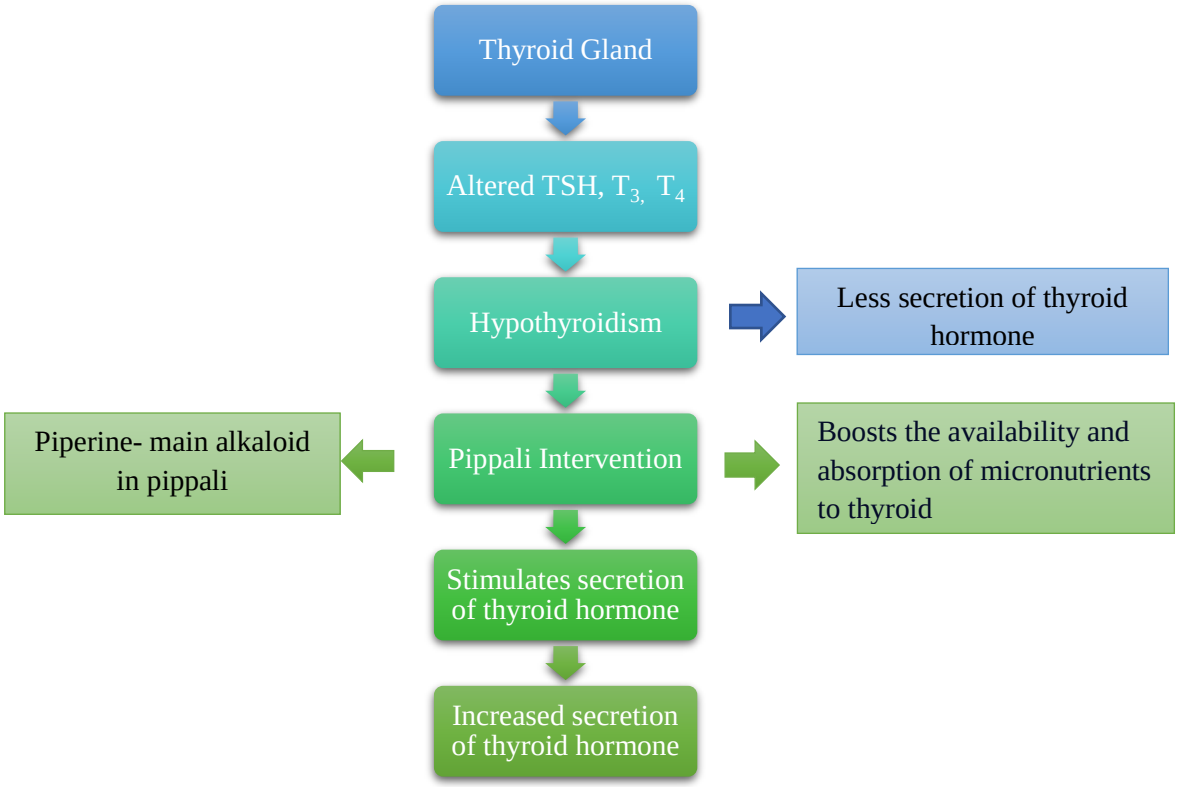
Thyroid Gland
Altered TSH, T_3, T_4
Hypothyroidism
Less secretion of thyroid hormone
Piperine- main alkaloid in pippali
Pippali Intervention
Boosts the availability and absorption of micronutrients to thyroid
Stimulates secretion of thyroid hormone
Increased secretion of thyroid hormone

Fig. 4 Mechanism of Action of Pippali

1.4 RESEARCH GAP

➢ LIMITED CLINICAL TRIALS

Few clinical trials have been conducted on the efficacy of pippali in improving hypothyroidism. Some studies were conducted on animals and only one on humans (Bhavin S et.al.2022)

➢ DOSAGE AND DURATION

In the present study the dosage to be provided in the intervention will be :

For the progressive group- It will be in increasing order starting from 0.5g to 7g.

For the fixed group- The dose will be given twice a day weighing 1.9g/ dose.

Clinical Trials- some trials suggested the following dose-

- 250-500 mg/day of pippali extract for 6-12 weeks.
- 1-2 g/day pippali powder for 12-24 weeks. (Dhikav, DM et al., 2019)

Ayurvedic Practices- some measurements are as under-

- ½-1 teaspoon pippali powder with warm water or milk twice a day.
- 10-20 ml/day of pippali kwatha (decoction.) (Kumar, S. et al., 2018)

➢ MECHANISM OF ACTION

Thyroid Hormone Regulation

1. Stimulation of thyroid gland: Pippali's piperine increases thyroid-stimulating hormone (TSH) receptors, enhancing thyroid hormone production.

2. Increased triiodothyronine (T3) and thyroxine (T4) levels: Piperine promotes conversion of T4 to T3.

3. Regulation of thyroid axis: Pippali modulates hypothalamic-pituitary-thyroid axis. (Dixit, H. et al., 2022)

Neuroendocrine Modulation

1. Stimulation of hypothalamic neurons: Pippali activates neurons producing thyrotropin-releasing hormone (TRH).

2. Regulation of dopamine and serotonin: Piperine influences neurotransmitters affecting thyroid function.

Potential Active Compounds

1. Piperine (primary bioactive compound)

2. Piperlongumine

3. Piperamide

4. Sesquiterpenes (Kumar, S. et al., 2018)

➢ DIVERSITY IN POPULATION

Existing studies often concentrate on narrow demographic groups. Future research should broaden its focus to encompass a variety of demographics, including age, gender, and ethnicity, to determine whether the effectiveness of pippali in treating hypothyroidism differs among these diverse groups.

➢ COMPARATIVE RESEARCH

There is a scarcity of studies that directly compare pippali with standard treatments or other herbal remedies for hypothyroidism. Conducting comparative efficacy research could yield important insights into the relative effectiveness of pippali in managing this condition.

1.5 SIGNIFICANCE OF THE STUDY

The significance of this research lies in addressing the health concerns associated with hypothyroidism in India, a country grappling with numerous lifestyle disorders. This condition typically arises from iodine deficiency, a common occurrence in many regions. According to data from the National Family Health Survey (NFHS) V conducted between 2019 and 2021, the self-reported prevalence of thyroid disorders stands at 2.9%. However, a research indicates staggering estimate of approximately 42 million individuals grappling with thyroid disorders across the nation. Some studies have been conducted to check the effect of pippali on hypothyroidism. The trials were conducted on the adult male mice and concluded that pippali boost the metabolism of the selected subjects (Panda S. et.al., 2003). Very few studies have been conducted on humans (Bhavin S. et. al.,2022) and none in North India. Pippali possesses VataeKaphahara with Agni deepana (Bio-fire enhancer) and Rasayana (Rejuvenating) properties which seems to be promising in Hypothyroidism. The essential nutrients and compounds present in long pepper are eugenol, glycosides, piperine, resins, sugar, saturated fat, essential oil, volatile oil, piplartine, myrcene, terpenoids, quercetin, triacontane, and sylvatine. The present study aims to fill this gap by investigating the potential of pippali, an Ayurvedic remedy, in improving thyroid functioning. By incorporating traditional Ayurvedic approaches, the research offers holistic solutions to manage thyroid disorders, potentially alleviating symptoms such as inflammation, obesity, slow metabolism, and hair thinning.

1.6 OBJECTIVES

- To identify diagnosed cases of hypothyroidism.
- To assess dietary intake and anthropometric variables of selected subjects.
- To intervene pippali powder in two different dosages and pattern among the subjects.
- To evaluate and compare the effect of intervention on hypothyroidism markers and subjective symptoms (zulewski’s score) of the subjects.

2. REVIEW OF LITERATURE

S. No.	Title of the study	Year of Study	Name of the author	Major findings
1.	Physiology, thyroid function	2023	Maggie Armstrong et.al., National Library of Medicine.	The thyroid produces approximately 90% inactive thyroid hormone, or thyroxine (t4), and 10% active thyroid hormone, or triiodothyronine (t3).
2.	Efficacy of pippali in vardhamana and fixed dosage pattern in primary hypothyroidism e a randomized clinical trial	2022	Shrey bhavin shah et.al., Journal of Ayurveda and Integrative Medicine.	Pippali is efficacious in reducing the signs and symptoms of primary hypothyroidism and also has a positive impact on the thyroid profile but is more effective when administered in vardhamana dosage compared to fixed dose.
3.	Piper longum L.: A comprehensive review on traditional uses, phytochemistry, pharmacology, and health-promoting activities	2022	Protha Biswas et.al., National Library of Medicine. 4425-4476	Many of its pharmacological properties were attributed to its antioxidative and anti-inflammatory effects and its ability to modulate some signalling pathways and enzymes.
4.	Piper longum (pippalimool): a systematic review on the traditional and pharmacological properties of the plant	2021	Manish Grover et.al., World journal of pharmaceutical and medical research. 281-287	The fruits are mostly used as culinary spices and preservatives and are also a potent remedy in various traditional medicinal systems against bronchitis, cough, cold, snakebite, and scorpion-sting and are also used as a contraceptive. Various bioactive-phytochemicals including alkaloids, flavonoids, esters, and steroids were identified from the plant extracts and essential oils from the roots and fruits.
5.	A systematic review on Piper longum L.: Bridging traditional knowledge and pharmacological evidence for future translational research	2020	Vaishali Yadav et.al., National Library of Medicine.	It exhibits a wide range of activities including anti-inflammatory, analgesic, anti-oxidant, anti-microbial, anti-cancer, anti-parkinsonian, anti-stress, nootropic, anti-epileptic, anti-hyperglycemic, hepatoprotective, anti-hyperlipidemic, anti-platelet, anti-angiogenic, immunomodulatory, anti-arthritic, anti-ulcer, anti-asthmatic, anthelmintic action, anti-amebic, anti-fungal, mosquito larvicidal and anti-snake venom.

6.	Zulewski's clinical score and its validation in hypothyroid patients. Experience in a tertiary care center in Western India	2020	Srivastava Prachi et.al., CHRISMED Journal of Health and Research. 16-19	Zulewski's clinical scoring is an economic and effective tool for identifying clinical hypothyroidism and can be used as a clinical basis for starting levothyroxine replacement therapy if due to unavoidable reasons, it is difficult to get a thyroid function test.
7.	Therapeutic benefits of long pepper (pippali)	2018	Dr luxita sharma et.al., 2018. International Journal of Creative Research Thoughts. 468-477	Piper longum was cultivated from the lower hills of bengal, the evergreen forests of the western ghats, uttar pradesh nicobar islands, and nepal. It is cultivated on a large scale in limestone soil, where dampness is high in heavy rainfall areas.
8.	A review article on Pippali	2015	Ashalatha M. et al., International Ayurvedic Medical Journal. 2848-2849	It is extensively used as an anti-inflammatory, cough suppressor, antibacterial, insecticidal, antimalarial, CNS stimulant, antitubercular, anti-helminthic, hypoglycaemic, antispasmodic, antigiardial, immunostimulatory, hepatoprotective, analeptic, antinarcotic, antiulcerogenic activity.
9.	Thyroid disorders in India: An epidemiological perspective	2011	Unnikrishnan G.K. et.al., An epidemiological perspective. S78-S81	The study focused on the epidemiology of 5 common thyroid diseases in India: hypothyroidism, hyperthyroidism, goiter and iodine deficiency disorders, Hashimoto's thyroiditis and thyroid cancer.
10.	A clinical trial of *Pippali* (*Piper longum* Linn.) with special reference to *Abheshaja*	2010	Megha Pathak et.al., National Library of Medicine. 2010 442-446	The drug *Pippali (Piper Longum* Linn.) has been contraindicated to be used for a longer duration.
11.	Piperine lowers the serum concentrations of thyroid hormones, glucose and hepatic 5'd activity in adult male mice	2003	Panda S et.al., Piperine lowers the serum concentrations of thyroid hormones, glucose and hepatic 5'D activity I n adult male mice.	The decrease in t (4), t (3) concentrations and in g-6-pase were comparable to that of a standard antithyroid drug, proylthiouracil (ptu). The hepatic lipid-peroxidation (lpo) and the activity of endogenous antioxidants, superoxide dismutase (sod), and catalase (cat) were not significantly altered in either of the doses.

12.	Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls	1997	H zulewski et.al., Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various grades of hypothyroidism and controls.	The clinical score was defined as the sum of the 2 best-discriminating signs and symptoms. Besides tsh and thyroid hormones, we measured parameters known to reflect tissue manifestations of hypothyroidism, such as ankle reflex relaxation time and total cholesterol

3. METHODOLOGY

3.1 STUDY DESIGN

It is a randomized clinical trial. The study population will be composed of subjects diagnosed with primary hypothyroidism selected from OPDs and IPDs of Saran Ashram hospital of Agra City. Ethical clearance will be taken from the Ethical Committee of Dayalbagh Educational Institute (Deemed University), Agra. Informed written consent will be taken from the patients enrolled in the study.

3.2 PARTICIPANT SELECTION

The subjects will be selected purposively based on the diagnosis of hypothyroidism. The participants will be chosen between the ages of 25-60 years.

SAMPLE SIZE

A total of 100 subjectss will be divided equally and randomly in a control group and the test group for pippali dosage implementation. This study is an improvisation and continuation (sample size and dosage) of the previous research done by Bavin. S. et.al. Sample size is kept lower since this a biochemical intervention strictly under the supervision of medical practitioner.

INCLUSION CRITERIA

- Subjectss in the age group of 25-60 years.
- Serum T3 (< 80 ng/dL) T4 (< 5.10 mg/dL) and TSH (> 4.20 mIU/dL) levels which indicate Subclinical or Overt Hypothyroidism
- Subjectss willing to be a part of the study.

EXCLUSION CRITERIA

- Subjects who had undergone any thyroid surgery.
- Subjects diagnosed with cardiac disorders, morbid obesity, uncontrolled diabetes, and carcinomas.

Subjects suffering from congenital or secondary hypothyroidism.

- Serum TSH levels more >20 mIU/dL.
- Pregnant and lactating women.

DIAGNOSTIC CRITERIA

The diagnosis will be made based on the presence of signs and symptoms of Hypothyroidism with Ser. TSH values > 5.0 mIU/ml with or without the decrease in serum T_3 and T_4 concentration.

LABORATORY INVESTIGATION

Thyroid profile (Ser. TSH, Total T_4, and T_3).

3.3 INTERVENTION

The intervention will be conducted in two phases i.e., phase I (Fixed Dosage) consisting of 1 control group and 1 test group and phase II consisting of 1 control group and 1 test group (progressive dosage group). The intervention will be done on same group of subjects in order to get the better comparsion of the result. The subjects will receive a standardized dose of pippali extract in powder form which will be administered orally based on the dosage pattern. The powder will be made under controlled and hygienic conditions in the "Food Testing Lab" of the Department of Home Science, Faculty of Arts, Dayalbagh Educational Institute, Agra.

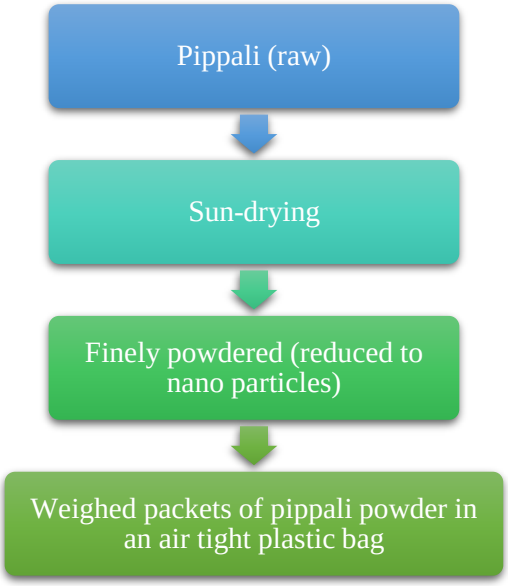
Pippali (raw)
Sun-drying
Finely powdered (reduced to nano particles)
Weighed packets of pippali powder in an air tight plastic bag

Fig. 5 Formulation of Pippali Powder

GROUP DIVISION

One control group and one test group (both the groups will be repeated for intervention phase II- progressive and fixed dosage patterns) with equal participants will be made. Each group will comprise 50 subjects. The groups will be allocated blindly. Subjects will receive the supplementation and will administer it along with the medication they are following under the strict observation of the General Physician and the Ayurvedic Doctor.

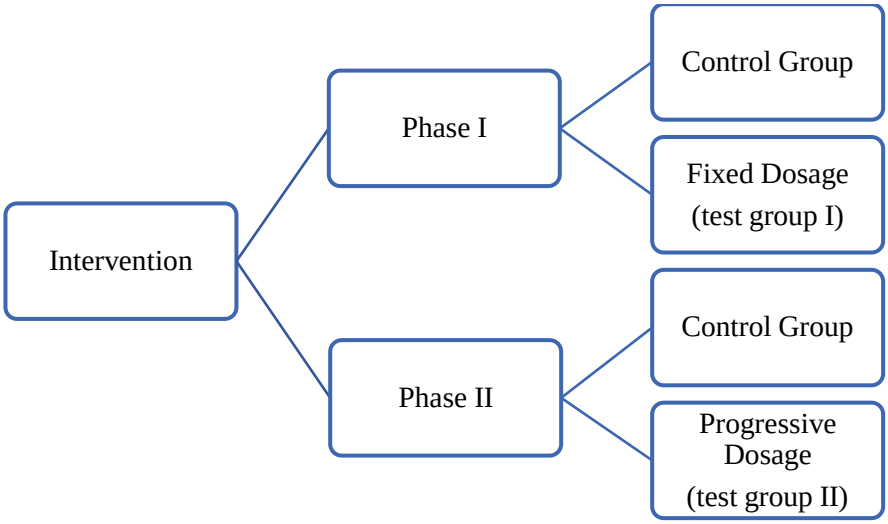

Fig. 6 Intervention plan

PROGRESSIVE GROUP

- 0.5g pippali powder will be given on day one on an empty stomach in the morning with 50 ml of milk.
- The dose of pippali will be gradually increased by 0.5g per day reaching a maximum of 7 grams till the 14th day.
- It will be reduced by 0.5g per day till the 27th day.
- Follow-up will be taken on the 45th day.

Table 3 Supplementation Plan

Increasing order		**Decreasing order**	
Day	**Dose**	**Day**	**Dose**
1	0.5g	15	6.5g
2	1g	16	6g
3	1.5g	17	5.5g
4	2g	18	5g
5	2.5g	19	4.5g
6	3g	20	4g

7	3.5g	21	3.5g
8	4g	22	3g
9	4.5g	23	2.5g
10	5g	24	2g
11	5.5g	25	1.5g
12	6g	26	1g
13	6.5g	27	0.5g
14	7g		

FIXED GROUP

A fixed dosage of 3.75 g Pippali powder will be given with 50 ml of milk in the morning on an empty stomach for 27 days. The dosage will be given twice daily, measuring 1.9g in the morning and 1.9 g in the evening. The subjects will be asked not to eat anything half an hour before and after administering the supplementation.

3.4 ASSESSMENT CRITERIA

- The degree of clinical hypothyroidism will be estimated using the score developed by Zulewski et al.
- Ser. TSH, T_3, and T_4 levels.
- Anthropometric measurement- weight, BMI, and body fat % will be taken on 0^{th} day, 28^{th} day, and 45^{th} day (follow up) for sustenance.

3.5 ASSESSMENT SCHEDULE

- Biochemical analysis for thyroid profile will be done for both the test groups on the 0^{th} and 28^{th} day.
- The sustenance effect of the herb will be checked on the 45^{th} day for both groups.
- Zulewski's analysis- Test result values of the thyroid profile of the patients will be compared to Zulewski's scores for the analysis.
- Data analysis- Data will be analyzed statistically for results and calculations.

4. LIMITATION

The study will be conducted in Dayalbagh area of Agra City.

5. PLAN OF STUDY→

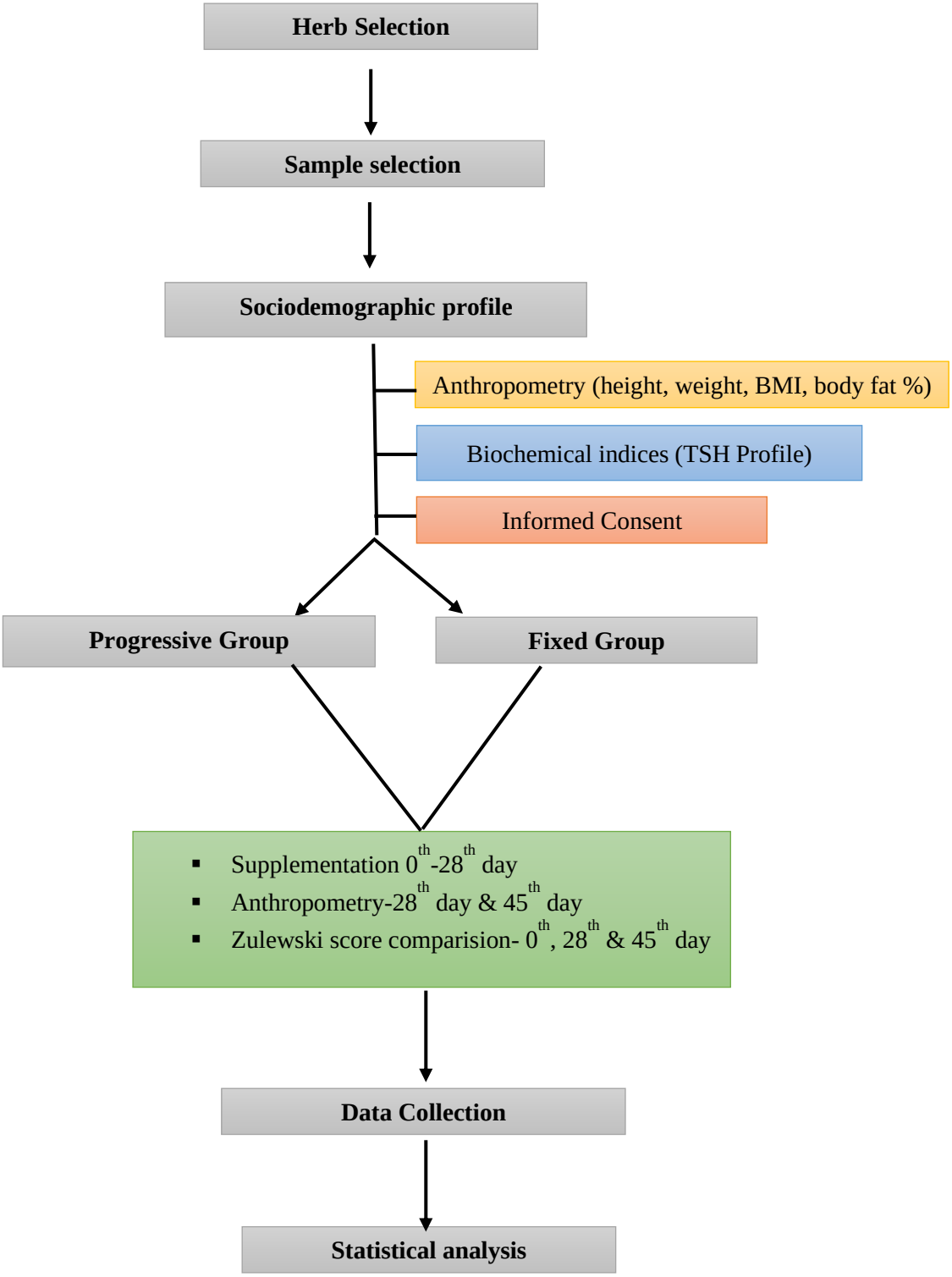

Fig. 7 Research Plan

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